

Special K: A review of Ketamine

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BACKGROUND

Ketamine was first synthesized in 1962 by Dr. Calvin Stevens of Wayne State University while at Parke Davis Laboratories.¹ His work at the time was investigating an alternative anesthetic to phencyclidine (PCP), less likely to cause seizures or neurotoxicity. As such, Ketamine is a dissociative anesthetic, similar in chemical structure to PCP, and produces anesthesia through hallucinogenic, amnestic, analgesic, sedative, and cataleptic effects. This is in contrast to other induction agents such as benzodiazepines, which produce anesthesia primarily through sedation.^{2,3}

Ketamine is a dissociative agent. It induces in the patient a state of detachment from the outside world, in which pain signals reach the brain but are not perceived, and the patient remains in a cataleptic trance, often with his or her eyes open. Consequently, Ketamine lacks a typical dose-response relationship, but must instead be given in a quantity sufficient to achieve this "dissociative threshold."⁴ Ketamine is unique among induction agents in that it provides analgesia in addition to amnesia and sedation. It has complex interactions with multiple biochemical receptors, including the NMDA receptor complex (neuroinhibition and anesthesia), opioid receptors (analgesia), and catecholamine receptors (inotropic and chronotropic effects).⁵⁻⁷ Ketamine has been used extensively as an anesthetic and sedative agent in both human and veterinarian medicine. It gained popularity in the 1970s in battlefield and burn medicine settings, and is also abused on the street.

MECHANISM

Ketamine acts upon a variety of targets, including N-methyl-D-aspartate (NMDA) receptors, opioid receptors, monoaminergic receptors, muscarinic receptors, and voltage-sensitive calcium channels. Ketamine's most notable properties are in large part from its effects on NMDA receptors. Ketamine noncompetitively antagonizes NMDA Ca²⁺ channel pores, and binds to NMDA receptors' phencyclidine (PCP) binding sites, collectively inducing significant NMDA receptor inhibition. As a consequence, the sensory association areas of the cortex, as well as parts of the limbic system and thalamus, are directly depressed by Ketamine. Because the limbic system integrates peripheral sensory signals from the thalamus, and is involved in memory development, Ketamine leaves the brain temporarily unable to process peripheral pain signals or assign them emotional meaning. As a result, while under Ketamine anesthesia, the patient is completely unaware of the outside world.^{4,8}

Ketamine also produces analgesia through nitric oxide (NO) synthase inhibition, which decreases levels of nitric oxide, a central and peripheral pain neurotransmitter. Additionally it has complex interactions with opioid receptors, but this interaction is not believed to produce significant analgesia. Furthermore, Ketamine blocks neuronal reuptake of catecholamines, and is thought to be a muscarinic receptor antagonist, which collectively produce anticholinergic effects such as delirium and bronchodilation, as well as sympathomimetic effects.^{4,8}

BENEFITS

Ketamine is rapid in onset (45 to 60 seconds) with peak effect in 1 to 5 minutes, has a relatively short duration of action (10 to 20 minutes), and has no adverse effects on respiratory drive, making it useful for "awake" intubations in difficult airway situations. It also preserves protective airway reflexes such as coughing and swallowing, and maintains the muscular tone of the pharynx and tongue.⁴

Ketamine stimulates bronchodilation, making it useful in asthmatic and bronchoconstricted patients. This effect is thought to occur through either sympathomimetic (beta₂ adrenergic agonist) stimulation, a direct relaxant or membrane-stabilizing effect, or antagonism to histamine or acetylcholine. However, the extent to which this bronchodilation is clinically significant is unclear, and evidence to support Ketamine as a bronchodilator is limited and conflicting.⁹⁻¹² For example, a 1996 randomized, double-blinded, placebo-controlled trial of intravenous Ketamine in acute asthma demonstrated no beneficial effect when compared with placebo.¹²

Ketamine's sympathomimetic properties make it the most hemodynamically stable choice among sedative induction agents.⁷ Along with Etomidate, it is an induction agent of choice for hypotensive patients and patients in various forms of shock.

LIMITATIONS

Ketamine is notorious for a "reemergence phenomenon" in which patients experience nightmares or delirium while awakening from Ketamine anesthesia. This side-effect can be blunted and often prevented by administering a benzodiazepine. A 2011 randomized controlled trial of 200 patients receiving Ketamine for procedural sedation demonstrated that when given 0.03 mg/kg of Midazolam IV, 8% of patients experienced the reemergence phenomenon (compared to 23% of those with Ketamine and placebo).¹³ No patients experienced respiratory depression, all patients experienced adequate analgesia, and no patients required additional dosing.

Controversy exists over whether Ketamine is a safe agent in head injured patients. Theoretically, as Ketamine has sympathomimetic effects, it will increase intracranial pressure. Advocates, however, have provided limited evidence that Ketamine does not increase ICP in head-injured patients in a controlled-ventilation setting. Furthermore, evidence suggests that giving Ketamine

in combination with a GABA agonist (such as Propofol) may actually decrease intracranial pressure.¹⁴

As a consequence of its sympathomimetic properties, Ketamine should be avoided as an induction agent in patients in status epilepticus and in patients with limited cardiac reserve.

Limited evidence suggests Ketamine may increase intraocular pressure. Other studies suggest it may instead decrease or have no effect on intraocular pressure.⁴ At this time, its use in patients with concern of increased eye pressures is also controversial.

While Ketamine preserves respiratory drive if given in appropriate clinical doses, rapid bolus IV pushes may produce respiratory depression.⁴

DOSAGE

Anesthetic dosage is 0.5-2 mg/kg I.V., or 4-10 mg/kg I.M.² These guidelines appear in large part to have originated from a 1980 Anesthesiology article performing a meta-analysis of effective Ketamine doses in a variety of surgical contexts.

EMS USE

Excited Delirium

Ketamine has been suggested as an ideal agent for excited delirium in the prehospital setting.¹⁷⁻¹⁹ Excited delirium syndrome is often violent and unpredictable, so Ketamine's ability to produce rapid and predictable sedation intramuscularly is beneficial in this circumstance.¹⁸ Several limited case series have reported efficacy.²⁰⁻²¹ A dose of 4 to 10 mg/kg IM has been suggested to rapidly produce 15 to 20 minutes of dissociation.¹⁷⁻¹⁸ The 15-20 minutes that ketamine provides will allow for soft restraints to be applied and patient to be transported to the emergency department for further evaluation. However, a paucity of literature exists to evaluate how Ketamine's sympathomimetic effects interact with a population that may be experiencing adrenergic surge, acidosis, and hyperdynamic vital signs. Another concern is that excited delirium patients are also at risk for head and or ophthalmic injury which may make ketamine use dangerous due to possible increases in intracranial or ophthalmic pressure. Nevertheless, Ketamine has been safely used as an anesthetic on patients with minimal monitoring in rural and international medicine settings for decades. One survey of 172 developing world physicians reported only one serious adverse outcome out of 12,844 administrations on patients who overwhelmingly had no cardiac monitoring or pulse oximetry.²² This suggests Ketamine may be among the safest choices to address excited delirium in the chaotic prehospital setting. Further research should be done to confirm prehospital use in excited delirium patients is efficacious and safe.

Pain Adjunct

Yet another possible use for ketamine includes it's use as an adjunct to narcotics in the treatment of pain. In the Journal of Palliative Medicine in 2012 an article was published addressing the use of ketamine in addition to narcotics and other agents to treat chronic pain. This article reviewed

several studies which provided evidence that ketamine is a useful anesthetic when given at subanesthetic doses (<1mg/kg) in patients with cancer, neuropathic or ischemic pain.²³ One article discusses four case reports where where ketamine was used for analgesia in the prehospital setting where prolonged extrication was required. One of these cases described a 32 year old man who was in a motor vehicle collision which left him with both of his lower extremities entrapped. This man was conscious, in severe pain, and required immediate resuscitation and extrication. A anesthetist was called to to the scene to provide anesthesia. Ketamine was the agent chosen, and it was used for four hours while the patient was successfully resuscitated and extricated.²⁴ There is another case report describing the use of intranasal ketamine (0.5mg/kg) in a 9 year boy who suffered burns to his trunk. The patient arrived at the hospital free of pain with stable vital signs.²⁵ A randomized controlled trial regarding the use of morphine along with ketamine in out of hospital trauma patients was recently published in the Annals of Emergency medicine. In this article IV morphine + IV ketamine was shown to be superior for treatment of pain when compared to morphine alone, yet was associated with increased minor adverse side effects which included disorientation.²⁶ The use of ketamine in trauma patients could be complicated considering it's association with increases in intracranial or ophthalmic pressure in the presence of trauma. Also an alteration in mental status may be mistaken for the progression of a head injury.

CONCLUSION

Ketamine is a dissociative agent that produces anesthesia through hallucinogenic, amnestic, analgesic, and cataleptic effects. It acts on multiple biochemical receptors, including the NMDA receptor complex, opioid receptors, and catecholamine receptors. It lacks a typical dose-response relationship and must be given in quantities sufficient to reach a "dissociative threshold." Ketamine is rapid in onset (45 to 60 seconds) and has a relatively short duration of action (10 to 20 minutes). It is among the most hemodynamically stable anesthetics and does not cause respiratory depression. Some evidence exists that ketamine maybe useful in the prehospital setting for sedation and analgesia. There are some drawbacks including: possible increase in intracranial pressure, increase in ophthalmic pressure, disorientation and possible emergence phenomenon. Further research is necessary to confirm safety of ketamine use in the prehospital setting.

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